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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/977,179	10/15/2001	Corrado Spadafora		2856

7590 03/09/2004

EXAMINER	
PARAS JR, PETER	

ART UNIT	PAPER NUMBER
1632	

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DATE MAILED: 03/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/977,179	SPADAFORA ET AL.	
	Examiner	Art Unit	
	Peter Paras, Jr.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 December 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *18 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *0104*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending.

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-17, in the response received on 12/16/03, is acknowledged.

Claims 18-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the response received on 12/16/03.

Drawings

New corrected drawings are required in this application because the drawings contain written text. Also, the background levels in Figure 4 render it illegible. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

Specification

The spacing of the lines of the specification is such as to make reading and entry of amendments difficult. New application papers with lines double spaced on good quality paper are required.

The claims are objected to because the lines are crowded too closely together, making reading and entry of amendments difficult. Substitute claims with lines one and one-half or double spaced on good quality paper are required. See 37 CFR 1.52(b).

Priority

The instant specification appears to claim the benefit of priority to a provisional application. However, the provisional application has not been identified by serial number and filing date. An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification or in an application data sheet (37 CFR 1.78(a)(2) and (a)(5)). Priority cannot be perfected until reference to the parent application is made.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for introducing nucleic acid molecules, particularly RNA, into human beings and non-human organisms comprising incubating RNA molecules with sperm cells, fertilizing an egg with the sperm cells, transferring said fertilized egg to a recipient host to produce offspring.

The specification discusses that the invention features methods for the production and use of transgenic multi-cellular organisms. See page 3. The specification discusses that the invention features methods of creating transgenic organisms by fertilizing eggs with sperm that have been incubated with RNA containing transgenes. See page 3 at the bottom. The specification suggests the invention relies on the capacity of sperm to reverse-transcribe exogenous RNA to cDNA, wherein the exogenous nucleic acid molecules are maintained episomally and do not integrate into the germline (see pages 3-4). While the specification provides extensive teachings, specific guidance, and working examples pertaining to the creation of a mouse comprising exogenous reporter gene sequences that are maintained episomally, the specification fails to provide any relevant teachings or specific guidance with regard to the generation of any transgenic organisms with their corresponding phenotypes embraced by the claims (as is consistent with the discussion of the specification). Furthermore, the specification fails to even describe any particular of phenotype exhibited by any of the transgenic organisms embraced by the invention, but only contemplates that such organisms (including humans) would be useful for treating hereditary diseases and cancer or for producing collectable proteins or nucleic acid molecules (see page 4 and also the claims). In view of the lack of guidance provided by

the specification it would have required undue experimentation to use the claimed method to produce transgenic organisms.

In addition, when analyzing the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest reasonable interpretation of the claimed methods is one that that results in the production of transgenic organisms that express a transgene at a level sufficient to result in a phenotype correlating either to production of proteins or nucleic acid molecules or to treatment of disease *(i.e.*, it is unknown what other purpose the transgenic organism would serve if the transgene is not expressed at a sufficient level for a resulting phenotype).

The claims embrace the creation of any transgenic organism. However, while the specification has provided working examples exemplifying the creation of a mouse comprising cells having a mosaic pattern of heterologous reporter gene expression, wherein the heterologous reporter sequences are maintained episomally and are not integrated into the mouse genome, the specification has failed to provide any relevant teachings, guidance, working examples with respect to the production of any transgenic organisms, whose genomes comprise any heterologous transgenes, as embraced by the claims. One of skill would not be able to rely on the state of the transgenic art for an attempt to produce transgenic organisms whose genomes comprise a heterologous transgene. This is because the state of the art of transgenics is not a predictable art with respect to transgene behavior and the resulting phenotype. While the state of the

art of transgenics is such that one of skill in the art would be able to produce transgenic organisms comprising a transgene of interest, it is not predictable if the transgene would be expressed at a level and specificity sufficient to cause a particular phenotype. For instance, the level and specificity of expression of a transgene as well as the resulting phenotype of the transgenic animal are directly dependent on the specific transgene construct. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the specificity of transgene integration into the genome, for example, are all important factors in controlling the expression of a transgene in the production of a transgenic animal which exhibits a resulting phenotype. This observation is supported by Wall (Theriogenology, 1996) who states that "[o]ur lack of understanding of essential genetic control elements makes it difficult to design transgenes with predictable behavior." See page 61, last paragraph. See also Houdebine (Journal of Biotechnology, 1994) who discloses that in the field of transgenics, constructs must be designed case by case without general rules to obtain good expression of a transgene (page 275, column 1, 1st paragraph); *e.g.*, specific promoters, presence or absence of introns, *etc.* As such, guidance is lacking in the instant specification for the production of transgenic organisms and their corresponding phenotypes embraced by the claims.

Furthermore, without evidence to the contrary, transgene expression in different species of transgenic non-human animals is not predictable and varies according to the particular host species, and specific promoter/gene combination(s). This observation is specifically supported by Hammer et al. (Journal of Animal Science, 1986) who report

the production of transgenic mice, sheep and pigs; however only transgenic mice exhibited an increase in growth due to the expression of the gene encoding human growth hormone (pages 276-277, Subsection: Effect of Foreign GH on Growth). The same transgene construct in transgenic pigs and sheep did not cause the same phenotypic effect. See also Ebert et al. (Molecular Endocrinology, 1988). This observation is further supported by Mullins et al. (Journal of Clinical Investigations, 1996) who report on transgenesis in the rat and larger mammals. Mullins et al. state that "a given construct may react very differently from one species to another." See page S39, Summary. Wall et al. report that "transgene expression and the physiological consequences of transgene products in livestock are not always predicted in transgenic mouse studies." See page 62, first paragraph. Kappel et al. (Current Opinion in Biotechnology, 1992) disclose the existence of inherent cellular mechanisms that may alter the pattern of gene expression such as DNA imprinting, resulting from differential CpG methylation (page 549, column 2, 3rd full paragraph). Strojek and Wagner (Genetic Engineering, 1988) pointed out that a high degree of expression of a transgene in a mouse is often not predictive of high expression in other species, including pigs and rabbits, because, for example, the cis acting elements may interact with different trans-acting factors in these other species (paragraph bridging pages 238-239). Given such species differences in the expression of a transgene, particularly when taken with the lack of guidance in the specification for the production of transgenic organisms, it would have required undue experimentation to predict the results achieved in any transgenic organisms and their corresponding phenotypes embraced by the claims.

The specification has taught the creation of a mouse comprising cells having a mosaic pattern of heterologous reporter gene expression, wherein the heterologous reporter sequences are maintained episomally and are not integrated into the mouse genome. In addition, to the general issues of unpredictability associated with transgenesis discussed above, it appears unpredictable if such a mosaic mouse could express a heterologous coding sequence at a level sufficient to result in a phenotype. A mosaic mouse comprises an undeterminable number of cells that comprise and express a transgene. Moreover, it does not appear that any reproducible pattern of transgene expression could be obtained in such a mouse since the transgene is maintained and expressed episomally. It appears that a transgene would be expressed in a different mosaic pattern in each mouse created by the claimed methods. See at the top page 6 of the specification, which teaches the heterologous "cDNA was distributed non-homogeniously with the organs [of a mouse created by the claimed methods]." Furthermore, while it appears the heterologous cDNA can be transmitted to progeny, no reproducible pattern of expression is observed in progeny. See page 6 of the specification in the paragraph entitled 'Preferred embodiment 2', which states "[heterologous] cDNA was detected with variable frequencies in all F1 animals, the cDNA shows a mosaic distribution within the organs of the same animal, some organs, more than others appear to be preferential targets for cDNA molecules." Given, the variability of expression patterns within organs of the described mosaic mouse it is unclear what the role of a tissue-specific promoter might be in a transgene construct as the random pattern of expression appears to be the result of the method of preparation

of the mouse as opposed to the transgene construct itself. In any event, Sciamanna et al (Biochemical and Biophysical Research Communications, 2003, 312: 1039-1046), corroborates the variability of transgene expression in a mosaic mouse created by claimed methods (see pages 1042-1043). Even more Sciamanna et al teach that the heterologous cDNA "sequences are maintained at low copy number" [by their being barely at or below the limit of resolution in Southern blot experiments of PCR-positive DNA samples]. See page 1044, column 1, in the first full paragraph. Finally, since the heterologous sequences are maintained episomally, the specification has failed to provide guidance with respect to the duration of the sequences in the cells of a mosaic organism. It appears the sequences are present in at least the F1 generation however, it is not known exactly through how many generations the sequences may be detected. This again points to the irreproducibility of the mosaic organisms produced by the claimed methods. Given the variable and low expression levels of the heterologous sequences in the mosaic mouse, it appears unpredictable if such levels of expression are sufficient to result in a useful phenotype (for example: for screening agents, for collecting proteins, or for treating a disease); there do not appear to be any uses, other than creating transgenic organisms, for the claimed methods; the specification has not provided guidance for use of any organism, which does not express a heterologous gene at a level resulting in a phenotype produced by the claimed methods. The guidance provided by the specification fails to correlate transgene expression levels observed in the exemplified mosaic mouse with any phenotype other than expression of the reporter gene, β-galactosidase. Moreover, the specification has failed to provide

guidance for use of any organism, produced by the claimed methods, that lacks a phenotype. Accordingly, it would have required undue experimentation to use the claimed invention given the lack of guidance provided by the specification with respect to a phenotype resulting from transgene expression in a mosaic organism.

Claims 15-16 recite use of the claimed methods for treating a disease, which clearly read on the art of gene therapy. Given the low levels of transgene expression observed in the exemplified mosaic mouse it is unpredictable if the claimed methods could result in levels of transgene expression sufficient to treat a disease.
It appears that the guidance provided by the instant specification fails to correlate use of the claimed methods with production of a therapeutic protein *in vivo* resulting in treatment or prevention of disease. Thus, as enablement requires the specification to teach how to make and use the claimed invention, the specification fails to enable the claimed methods for treating or preventing disease.

The claims, particularly claims 15-16, embrace methods of treating or preventing a disorder in a subject by producing a therapeutic protein and clearly fall into the realm of gene therapy. While it should be noted the claims are not limited to any particular disorder or therapeutic gene, the specification has contemplated treating or preventing diseases such as cystic fibrosis, by the *in vivo* introduction of a therapeutic gene, such as the human CFTR gene, but has not provided any specific guidance or working examples that correlate to treatment of any disease. Since the instant specification has failed to provide specific guidance or working examples correlating to treatment of a disease one of skill in the art could not rely on the state of the gene therapy art to treat

any disease by way of the claimed methods. This is because the art of gene therapy is an unpredictable art with respect cell targeting, and levels of expression of a therapeutic protein necessary to provide therapy. The general relevance of these issues is apparent given the random expression pattern and low expression levels of heterologous cDNA sequences in the exemplified transgenic mouse as discussed above. It is unpredictable if a heterologous gene expression by way of the claimed methods would be sufficient to result in a therapeutic effect given the apparent given the random expression pattern and low expression levels of heterologous cDNA sequences in the exemplified transgenic mouse as discussed above. Such issues are discussed by two published reviews. Verma *et al.* teach that as of 1997, "there is still no single outcome that we can point to as a success story" (page 239, col. 1). The authors go on to state, "Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression" (page 239, col. 3). Anderson (1998) states that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of a human disease" (page 25, col 1) and concludes, "Several major deficiencies still exist including poor gene expression [after genes are delivered]" (page 30). Besides the general expectation that it will require years of further research to develop effective gene therapy (Anderson, page 30), it would require extensive research to understand the fundamental biology of the system. Furthermore, the specification has not provided any specific guidance or teachings with regard to the tissue-specific expression or expression levels of a therapeutic gene necessary to provide a therapeutic effect. Deonarain (1998, Expert Opin. Ther. Pat., Vol. 8, pages

53-69) indicate that one of the biggest problems hampering successful gene therapy is the "ability to [introduce] a gene into a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (page 240, sentence bridging columns 2 and 3). In light of the teachings of Anderson, Verma and Deonarain, it appears expression of a heterologous gene in a target cell is a critical element for successful gene therapy. However, the specification fails to provide guidance with respect to achieving cell-specific expression through the use of tissue-specific promoters or regulatory elements as suggested by the random pattern of heterologous DNA expression in the exemplified mosaic mouse (as discussed above). Given the lack of guidance provided by the specification it would have required undue experimentation to use the claimed methods for treating or preventing diseases.

It should be noted that although the publication date of these cited references is prior to the filing date of the instant application, the issues regarding the unpredictability of gene therapy remain the same and have not be resolved by the guidance provided by the instant specification.

Therefore, in view of the quantity of experimentation necessary to determine the parameters listed above for the production of transgenic organisms, the lack of direction or guidance provided by the specification for the production of transgenic organisms, the absence of working examples which demonstrate or correlate to the production of a transgenic organism, the unpredictable state of the art with respect to transgene

behavior in transgenic organisms, the unpredictable state of the gene therapy art, and the breadth of the claims drawn to all organisms, it would have required undue experimentation for one skilled in the art to make and/or use the claimed invention.

Claim Rejections - 35 USC § 112, 2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is indefinite as written. Step (g) is directed to identifying offspring expressing the desired traits of the introduced genes. The claim is indefinite because the meaning of "expressing the desired traits of the introduced genes" is unclear. The specification has not provided a definition of desired traits of genes or how an organism could express such traits. Usually, [phenotypic] traits result from expression of a [trans]gene as opposed to a gene itself having traits that are expressed by an organism. Appropriate correction is required.

Claim 1 is confusing as written. The claim is confusing because the first step is (c) while steps (a) and (b) appear to have been inadvertently omitted.

Claim 1 recites the limitation "the appropriate host species" in line 1 of step (h). There is insufficient antecedent basis for this limitation in the claim.

Claim 1 recites the limitation "the desired traits" in line 1 of step (g). There is insufficient antecedent basis for this limitation in the claim.

Claim 10 recites the limitation "the resulting transgenic organisms" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 11 recites the limitation "the resulting organisms" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 recites the limitation "the resulting transgenic organisms" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Regarding claim 12, the phrase "such as" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d). The phrase "as RNA, DNA or virus particles" is interpreted to mean "such as RNA, DNA, or virus particles". In event the claims recite parenthetical information and it is unclear whether such is part of the claimed invention.

Claim 13 recites the limitation "the resulting transgenic organisms" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 16 recites the limitation "the genes" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "the transmitted foreign genes" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "the transgene" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 17 recites the limitation "the affected cells" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claims 10-17 are rejected for being improperly dependent on claim 1. It is not clear if or how the starting materials or method steps are further limited.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Peter Paras, Jr., whose telephone number is (571) 272-0732. The examiner can normally be reached Monday-Friday from 8:30 to 4:30 (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached at 571-272-0804. Papers related to this application may be submitted by facsimile transmission. Papers should be faxed via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Official Fax Center number is (703) 872-9306.

Inquiries of a general nature or relating to the status of the application should be directed to Dianiece Jacobs whose telephone number is (571) 272-0532.

Peter Paras, Jr.

Art Unit 1632

PETER PARAS, JR.
PRIMARY EXAMINER